that of humans, the short allele is associated with decreased serotonergic function (lower CSF 5-HIAA concentrations) among monkeys reared in stressful conditions, but not among normally reared monkeys. Third, human neuroimaging research suggests that the stress response is mediated by variations in the 5-HTTLPR. Humans with one or two copies of the short allele exhibit greater amygdala neuronal activity to fearful stimuli compared to individuals homozygous for the long allele.

BRIEF SUMMARY OF THE INVENTION

[0011] The present invention relates, in part, to diagnostic methods for assessing whether a human or a non-human subject is predisposed to a mental disorder phenotype associated with an allele of a brain-functional gene, where a pathogenic environmental risk factor moderates the association between the allele and the phenotype. It is important in the methods to ascertain whether a subject assessed for predisposition to the disorder phenotype has either or both of the contributing genetic and environmental risk factors, or is vulnerable to the environmental risk factor. Similarly, it is important to ascertain the likelihood that a disorder phenotype seen in a subject arises as a result of genetic or environmental influences or both.

[0012] Results obtained from such a diagnostic method are advantageously employed in developing appropriate interventions for the subject, prior to or subsequent to the subject experiencing the pathogenic environmental risk factor, or both. In either case, the appropriate pre-emptive or therapeutic intervention can be adjusted in keeping with the findings of the diagnostic methods. At least two related scenarios are envisioned. Pre-emptive interventions designed to prevent or minimize exposure to the environmental pathogen can include counseling a subject to avoid the pathogen, or, if that is not possible, providing the subject with a pre-emptive treatment strategy when the pathogen is apparent. Therapeutic interventions after exposure to the pathogen can include pharmacological therapy and counseling therapy. One can also select one or more populations of individuals for participation in a pharmaceutical screening protocol on the basis of a combination of the genotype and experience with the pathogenic environmental risk factor by the individuals.

[0013] In another aspect, the present invention is summarized in that in a first diagnostic method for assessing predisposition of a subject to a disorder phenotype having an association with an at-risk allele of a brain-functional gene, the association being conditioned by a pathogenic environmental risk factor status condition, where the subject that has experienced, or is at risk of experiencing, the environmental risk factor, the method includes the steps of determining whether the subject carries one or more copies of an at-risk allele, and concluding that the subject is predisposed to the phenotype if the subject carries the at-risk allele.

[0014] In a related aspect, the present invention is summarized in that in a second diagnostic method for assessing predisposition of a subject to a disorder phenotype having an association with an at-risk allele of a brain-functional gene, the association being conditioned by a pathogenic environmental risk factor status condition, where the subject carries the at-risk allele, the method includes the steps of determining whether the subject has experienced or is at risk of experiencing the environmental risk factor, and concluding that the subject is predisposed to the phenotype if the subject has experienced or is at risk of experiencing the environmental risk factor.

[0015] In yet another related aspect, the present invention is summarized in that in a third diagnostic method for assessing predisposition of a subject to a disorder phenotype having an association with an at-risk allele of a brain-functional gene, the association being conditioned by a pathogenic environmental risk factor status condition, the method includes the steps of determining whether the subject carries the at-risk allele and determining whether the subject has experienced or is at risk of experiencing the environmental risk factor, the subject being predisposed to the phenotype if the subject carries the at-risk allele and has experienced or is at risk of experiencing the environmental risk factor.

[0016] The invention also relates to methods for discovering, in the first instance, a conditional association between an allele of a brain-functional gene and a mental disorder phenotype, where the association is conditioned upon a pathogenic environmental risk factor status, such a conditional association being suitable for evaluation in the diagnostic and preventative methods of the invention. One can employ the identified at-risk allele of a brain-functional gene and pathogenic environmental risk factor in any of the disclosed diagnostic methods for assessing whether an individual is predisposed to the associated disorder phenotype.

[0017] In a related aspect, such a discovery method includes the steps of identifying at least one a mental disorder phenotype having high or very high heritability coefficient, identifying a pathogenic environmental risk factor that operates on the at least one phenotype via non-genetic means and having at least higher and lower risk status conditions; ascertaining in a population of individuals an allelic profile for at least one brain-functional gene having an at-risk allele and at least one other allele, and selecting from the at least one disorder phenotype a disorder phenotype that correlates with statistical significance in the population with the at-risk allele only under the higher risk status condition, but which lacks statistically significant correlation with the at-risk allele under the lower risk status condition.

[0018] Methods for identifying a conditional association between an allele and a disorder phenotype, where the association is conditioned by a pathogenic environmental risk factor status condition, employ the well-characterized method of moderated multiple regression analysis to test for statistical interaction effects. See, Aiken, L. S. and S. G. West, *Multiple regression: Testing and Interpreting Interactions*, Thousand Oaks, Calif.: Sage (1991) and Long, S. J., *Regression Models for Categorical and Limited Dependent Variables*, Thousand Oaks, Calif.: Sage (1997), both incorporated by reference as if set forth herein in its entirety. Accordingly, it will be apparent that the present invention disclosure puts into the hands of the skilled artisan the ability to construct a matrix in which any or all of a plurality of pathogenic environmental risk factors, disorder phenotypes, and known alleles of brain-functional genes can be evaluated as described herein, preferably using a computing device for routine computations, to identify other conditional interactions between alleles and disorder phenotypes,